CHAPTER 8
INTERPRETATION AND IMPLICATIONS

An increasing number of patients with bone and joint tuberculosis (BJTB), including spinal tuberculosis (TB), has been seen in the Netherlands in recent years, raising our orthopaedic interest in TB. In Chapter 2 an analysis was made of this increased incidence. All data were extracted from the Netherlands Tuberculosis Register (NTR) held by the Royal Netherlands Tuberculosis Association KNCV. This unique register contains data on over 95% of all TB patients in the Netherlands from 1993. Between 1993 and 2000, a total of 532 patients with BJTB were registered, 308 (58%) with spinal lesions. This is in accordance with the percentages in the literature.

There was no significant change in the incidence of BJTB in the native Dutch population during the study period. Univariate analysis showed that the increase in incidence was restricted to foreign nationals from endemic areas. They constituted a relatively larger proportion of people with BJTB and spinal TB. The fact that certain ethnic groups showed a significantly higher chance of developing BJTB surprised us. This means that, with the same infection prevalence, some ethnic groups progress more often to BJTB, suggesting a genetic component in TB expression. A detailed genetic analysis might shed new light on this issue. Regarding the genetics of the micro-organism, DNA type clustering of the different strains of *M. tuberculosis* did not reveal any association between certain strains and BJTB.

The study demonstrated that only 15% of BJTB patients also suffered from pulmonary TB. The routinely taken chest radiograph hardly contributes in differential diagnostics and may never be used to exclude the possibility of spinal TB in differential diagnostics. We cannot compare the Dutch situation to neighbouring countries, as there are no recent reports on this topic in the literature.

The epidemiological analysis revealed a 3-month doctors' delay in diagnosis for spinal TB. This clearly demonstrates that many physicians in the Netherlands have a problem diagnosing spinal TB. The potentially devastating consequences of misdiagnosis are illustrated in Chapter 3. Two patients are reported who were misdiagnosed as having malignant lesions of the spine instead of TB. Both received radiotherapy, both experienced growth of the lesion, and in one patient the neurological deficit increased and did not reverse after initiation of the proper TB treatment.

The most common diagnosis in patients with spinal lesions of unknown origin is obviously metastasis. To prove the metastatic origin of a lesion screening is done for primary lesions like carcinoma of the prostate, lung or breast. If the primary lesion is revealed, radiation therapy is started. If not, biopsy is mandatory to confirm malignancy and exclude TB before radiation therapy is started. Radiation

is an aggressive and potentially harmful therapy that locally aggravates TB, as was demonstrated by our cases. The local immune response is indispensable in conquering the lesion; radiation severely affects this local response.

The diagnostic pathway should start with a thorough anamnesis and past medical history, which is simple and very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk group like immigrants from endemic countries, people with previous TB or people using immunosuppressive medication. Work-up often comprises a Mantoux test. Whether a positive test is helpful in diagnosis if patients are immigrants from endemic countries or born in a period when TB was very common is questionable; a positive Mantoux test may be proof of active disease as well as of previous exposure. Laboratory tests are not specific either. Radiographs and especially MRI are very helpful in diagnosing spinal TB. Typically, affected vertebral bodies on both sides of a destroyed disc are found; vertebral collapse and abscess formation can be seen too. However, the only definite proof of TB is a positive culture of material from the lesion. Because even a negative culture does not exclude TB and cultures may take up to 10 weeks before the results are known, histology is often mandatory. A newer means of proving TB is a molecular diagnostic technique called polymerase chain reaction (PCR). It is a nucleic acid amplification technique that shortens the time required to detect and identify *M. tuberculosis*. This technique does not replace the need for routine acid fast bacilli smear or culture, but it can greatly improve confidence in the clinical diagnosis pending culture results. If trochar biopsy fails to deliver a sufficient amount of material for examination, surgery is indicated. Surgery can provide sufficient biopsy material for histology and cultures, as well as instant decompression of the spinal cord.

The main reasons for the lengthy delay in diagnosis and misdiagnosis of spinal TB are low incidence, low index of suspicion, declined expertise and accepted failed biopsy. It is difficult to educate the patients about spinal TB, but we can at least try to promote awareness among our colleagues. Perhaps a nationwide panel of experts should be formed to advise about difficult cases. Spinal TB patients should be referred to centres of excellence where multidisciplinary care can be provided.

The length of treatment for spinal TB is commonly longer than the standard short-course 6-months used for other forms of TB. Clinical practice in the Netherlands is chemotherapy from six to more than 13 months. There is no uniform advise regarding length of treatment for spinal TB in the literature. Since compliance is important to prevent the emergence of resistant strains of *M. tuberculosis*, length of treatment should be no longer than strictly necessary. To assess whether the short-course 6-month treatment is as good as longer treatment regimens (> 6 months), we performed a review of the English, German, and French literature in Chapter 4. Outcome was evaluated in terms of relapse rates after successful treatment.

No randomised controlled trials were identified. Reasons for choosing the length of treatment were not stated. There were four publications with the short-course 6-month treatment regimen with a total of 82 adult patients. All the patients had undergone surgical intervention. After treatment completion, all the patients were declared cured. The relapse rate was 0%. There were 10 publications with a > 6-month treatment regimen, with a total of 274 patients. A proportion of the patients had undergone surgical intervention (162/274). Before completing treatment eight of 245 patients died, seven from unrelated causes and one from TB. A total of 93% were cured (227/245). Relapse occurred in 2% (4/218).

No differences were identified between 6 and >6 months regimens. There were no differences between the several regions of the world in characteristics of participants or outcome. The relapse rates were comparable. The fact that surgery was performed may have contributed to the low rate of relapse, although other studies done before the introduction of Pyrazinamide (1978), showed no statistically significant differences between operated and non-operated groups on relapse in spinal TB treatment.

Regarding the role of surgery, it seems logical that debridement or resection of the diseased tissue speeds up recovery. It diminishes the bacterial load the medication has to take care of, and the medication is delivered better because the necrosis, with its absence of vascularity, is gone. At present, we are planning a trial to evaluate local TB activity with positron emission tomography (PET). This will hopefully enable us to critically and precisely follow the result of treatment and it may even show that the length of chemotherapy treatment can be reduced further. The role of surgery in this aspect can be assessed too. This can typically be the kind of research that a high-tech country like the Netherlands can perform to contribute to the general knowledge of TB treatment.

Another means of shortening treatment duration may be the development of new medication. The last major drug introduced was Pyrazinamide, more than 25 years ago. Apparently TB is not an interesting disease for the pharmaceutical companies. This is the consequence of our economically-driven system: when there is little money to earn, stockholders cannot be satisfied and research agendas are set in other, more lucrative, directions. Of course, TB is mainly a disease of the poorer parts of the world, but patient numbers are still increasing and 2,000,000 people die annually from TB! It is crystal-clear that new medication is needed desperately.

One of the problems in spinal TB is the development of psoas abscesses that can become very large. It is questionable whether chemotherapy reaches sufficiently high concentrations inside fluid collections like psoas abscesses and pleural fluid. The intralesional concentrations of Isoniazid (ISO), Rifampicin (RIF) and Pyrazinamide (PYR) are not known. Insight into drug penetration is important since

sub-therapeutic drug concentrations may result in selection of a resistant bacterial population and lead to treatment failure. We performed a study (Chapter 5) on the concentrations of ISO, RIF and PYR inside psoas abscesses and tuberculous pleural effusions to gain insight into the actual intralesional concentrations in order to verify the possibility of sterilising lesions by chemotherapy alone. Concentrations in serum, pleural effusion (6 patients) and psoas abscess fluid (10 patients) were determined. They were below minimal inhibitory concentration (MIC) values in none of 15 patients for ISO, in 2 of 13 for RIF, and in 8 of 9 for PYR. The ratio of the maximal concentration (Cmax) to the MIC is a measure for the potency of a drug; a Cmax: MIC-ratio > 4 is indicative of effectiveness. This ratio was always greater than 4 for ISO, in 4 of 13 for RIF, and in none of 9 for PYR. In 5 of 8 patients receiving all three drugs, both RIF and PYR had Cmax:MIC ratios below 4, indicating intralesional sub-therapeutic drug levels. This local monotherapy with ISO carries the risk of selection of resistant bacterial populations and subsequent failure of treatment. Seven percent of TB patients in the Netherlands in 2000 in whom positive cultures were found had resistance to ISO.

We use percutaneous techniques to drain pleural effusions. In psoas abscesses, percutaneous drainage or even surgical debridement is advised to reduce the intralesional bacterial load and shorten the time to resolve the lesions. Diminishing the bacterial load may help reduce the chance of formation of drug resistance. Even the length of medical treatment may be reduced, thereby probably increasing compliance. This will further decrease the chance of formation of resistant strains. Drainage or surgical debridement is strongly advised as additional therapy for patients with pleural effusion or psoas abscesses.

Treatment in general for TB is aimed at completing the course of medication and prevention of relapse. Because of the special problems spinal TB poses, treatment must not only be aimed at local control and prevention of relapse, but also at prevention of deformity, pain and paraplegia. It must be multidisciplinary. Potential benefits of surgery in spinal TB are less kyphosis, a higher percentage of bony fusion, quicker relief of pain, immediate relief of compressed nerve tissue, quicker bony fusion and fewer relapses. The exact benefits of surgery are however not clear and there is ongoing controversy about the role of surgery since the 1960s. Surgeons promote surgery and non-surgeons state that chemotherapy alone is sufficient. The goal of Chapter 6 was to perform a systematic Cochrane review of the literature to compare chemotherapy to chemotherapy plus surgery, to evaluate the best evidence assessing the role of surgery.

Two randomized controlled trials (331 participants) met the inclusion criteria. They were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of

participants available for analysis at several time points. There was no statistically significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

Data are insufficient to be clear whether chemotherapy plus surgery is better than chemotherapy alone (with surgery used when clinically indicated). The investigated trials were performed some years ago, and current medication and operative techniques are far more advanced. However, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial.

Clinicians may judge that surgery may be indicated in subgroups of patients with an initial kyphosis angle greater than 30° (especially in children) or progressive or persistent neurological deficit with spinal cord compression despite chemotherapy but there are no randomized comparisons to support this. Future trials need to assess routine surgery and need to be large enough to assess outcomes properly. They need to assess pain and the patient's view of their disease and treatment. These trials also need to address subgroups of patients with spinal tuberculosis to establish the role of surgery for specific indications.

It would be ideal to identify at an early stage subgroups of patients likely to benefit from surgery. The surgical procedure is much easier to perform at an early stage of the disease, when less deformity has to be corrected. In Chapter 7 we evaluated radiographic and clinical parameters as early predictors for the final kyphotic angle.

Univariate analysis revealed no significant independent predictors. Multivariate analysis showed that indexed bone loss > 0.3 in combination with a thoracolumbar localisation indicated a 38% chance of non-favourable outcome (progression >10 degrees and/or a final angle > 40 degrees) versus only 3% when bone loss was ≤ 0.3 in combination with a thoracic localisation. The area under the receiver operating curve of this final model was 0.74, indicating an adequate predictive performance. A simple and clinically useful algorithm for early prediction of kyphosis in spinal TB was developed which identifies at an early stage of spinal TB those patients at risk of unfavourable outcome as well as patients who will very likely have a favourable outcome.

Our goal was to predict which patients are at risk of an unfavourable outcome, but it turned out that we were better in predicting favourable outcome! We recommend use of the algorithm to guide clinical decision-making.

Treatment can be started conservatively for all patients with kyphotic angles smaller than 40 degrees, but one can monitor extra carefully those patients with initial bone loss >0.3 in combination with a thoracolumbar localisation. Future investigations in larger populations may provide further fine-tuning of the algorithm to optimise individual treatment.